

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 20 JUN 2006

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Applicant's or agent's file reference PC32134A	<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. PCT/IB2005/000872	International filing date (day/month/year) 01.04.2005	Priority date (day/month/year) 13.04.2004	
International Patent Classification (IPC) or national classification and IPC INV. C07C255/54 C07C323/41 C07D317/58 C07D307/79 C07D285/14 C07D311/76 C07D209/16 C07D471/04 A61K31/277 A61P5/28			
Applicant WARNER-LAMBERT COMPANY LLC			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 4 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand  02.06.2005		Date of completion of this report  21.06.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer  Zervas, B  Telephone No. +31 70 340-3667	



**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2005/000872

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
  - ☐ international search (under Rules 12.3(a) and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4(a))
  - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements**\* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

**Description, Pages**

1-114 as originally filed

**Claims, Numbers**

1-15 received on 12.09.2005 with letter of 12.09.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

\* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**INTERNATIONAL PRELIMINARY REPORT  
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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,  
☒ claims Nos. 10 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 10 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).
- ☒ no international search report has been established for the said claims Nos. 10 (with respect to industrial applicability)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
  - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
  - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.  
PCT/B2005/000872

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	2,4,7,10-15
	No: Claims	1,3,5,6,8,9
Inventive step (IS)	Yes: Claims	2,4,7,10-15
	No: Claims	1,3,5,6,8,9
Industrial applicability (IA)	Yes: Claims	1-9, 11-15
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: WO 02/060896 A (PFIZER PRODUCTS INC; CHAMBERS, ROBERT, JAMES; MAGEE, THOMAS, VICTOR; M) 8 August 2002 (2002-08-08)  
D3: EP-A-0 002 309 (IMPERIAL CHEMICAL INDUSTRIES PLC) 13 June 1979 (1979-06-13)  
D4: WO 03/065992 A (GTX, INC; STEINER, MITCHELL, S; VEVERKA, KAREN, A; MILLER, DUANE, D; D) 14 August 2003 (2003-08-14)

**1. Novelty**

**1.1** The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 3, 5, 6, 8 and 9 is not new in the sense of Article 33(2) PCT. The document D1 (see D1, pages 215 - 219, examples 9, 11, 13, 15 and 16) disclose 2-(4-cyano-3-fluoro-phenoxy)-propionic acid derivatives which fall within the scope of the present claims 1, 3, 8 and 9 ( $R^1$  represents a methyl group and  $R^2$  is hydrogen). The document D3 (see D3, example 3) describes 3,4-dicyano-(2-hydroxy-2-methylpropionylamide which falls within the scope of the present claims 1, 3, 5 and 6 ( $R^1$  and  $R^2$  represent both a methyl group).

**1.2** The subject-matter of claims 2, 4, 7 and 10 - 15 appears to be novel with regard to the available prior art.

## **2. Inventive Step**

**2.1** The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 3, 5, 6, 8 and 9 does not involve an inventive step in the sense of Article 33(3) PCT.

Since the subject-matter of claims 1, 3, 5, 6, 8 and 9 is not novel, it cannot be regarded as inventive either.

**2.2** To the subject-matter of claims 2, 4, 7 and 10 - 15 the following applies:

Document D4, which discloses selective androgen modulators is regarded as representing the closest prior art. In view of D4 the problem underlying the present application can be defined as providing further selective androgen modulators. To solve this problem the applicant provides the compounds according to the present application, which differ from the compounds disclosed in D4 in the chain which is attached to the 4-position of the 1-cyano-2-trifluoromethyl-phenyl ring. Since the prior art does not disclose or suggest the -O-(CR<sup>1</sup>R<sup>2</sup>)-(Alk<sup>1</sup>)<sub>n</sub>-C(O)-Y chain described in the present application in relation with selective androgen modulators, the provision of the compounds of the present application as further selective androgen modulators is regarded as not obvious and does involve an inventive step in the sense of Article 33(3) PCT.

## **3. Industrial Applicability**

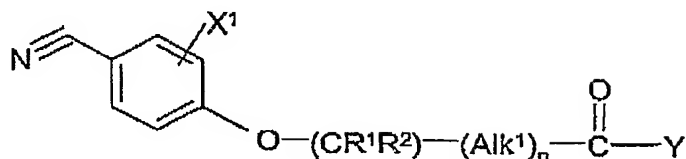
**3.1** The subject-matter of claims 1 - 9 and 11 - 15 is industrial applicable.

**3.2** For the assessment of the present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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## CLAIMS

1. A compound of the formula:



in which;

- a)  $X^1$  is represented by cyano, halogen or haloalkyl,
- b) one of  $R^1$  or  $R^2$  is represented by  $C_1$ - $C_6$  alkyl which may be optionally substituted, and the other of  $R^1$  or  $R^2$  is represented by hydrogen or  $C_1$ - $C_6$  alkyl which may be optionally substituted,
- c)  $Alk^1$  is represented by a  $C_1$ - $C_2$  linear alkylene group, in which up to two hydrogen atoms are optionally replaced by a substituent selected from the group consisting of  $C_1$ - $C_6$  alkyl optionally substituted, halogen, hydroxy, thiol, and cyano,
- d)  $n$  is represented by the integer 0 or 1,
- e)  $Y$  is represented by  $NX^2X^3$  or  $O-X^3$ ,
- f)  $X^2$  is represented by hydrogen or  $(C_1$ - $C_6)$  alkyl optionally substituted,
- g)  $X^3$  is represented by
  - i. hydrogen,
  - ii.  $(C_1$ - $C_{12})$  alkyl, optionally substituted,
  - iii.  $(C_2$ - $C_{12})$  alkenyl, optionally substituted,
  - iv.  $(C_2$ - $C_{12})$  alkynyl, optionally substituted,
  - v.  $(C_3$ - $C_{10})$  cycloalkyl, optionally substituted,
  - vi.  $(C_3$ - $C_{10})$  cycloalkyl( $C_1$ - $C_6$ ) alkyl, in which the alkyl and cycloalkyl moieties may each be optionally substituted,
  - vii.  $(C_6$ - $C_{10})$  aryl, optionally substituted,

- viii.  $(C_8-C_{10})\text{aryl}(C_1-C_6)\text{alkyl}$ , in which the alkyl and aryl moieties may each be optionally substituted,
- ix.  $-(CH_2)_q-(Alk^2)-C(O)R^3$ , in which  $Alk^2$  is represented by a  $(C_1-C_8)$  linear alkylene group, in which up to eight hydrogen atoms may optionally be replaced by a substituent, selected from the group consisting of  $(C_1-C_6)$  alkyl optionally substituted,  $(C_1-C_6)$  alkoxy, halogen, hydroxy, thiol, cyano, and  $NR^8R^9$  in which  $R^8$  and  $R^9$  are each independently represented by hydrogen or  $(C_1-C_6)$  alkyl,  $q$  is the integer 0 or 1,  $R^3$  is represented by hydrogen,  $(C_1-C_{12})\text{alkyl}$ ,  $(C_6-C_{10})\text{aryl}$ , or  $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkyl}$ , in which the alkyl and aryl moieties may each be optionally substituted,
- x.  $-(CH_2)_q-(Alk^2)-C(O)-O-R^4$ , in which  $Alk^2$  and  $q$  are as defined above, and  $R^4$  is represented by hydrogen,  $(C_1-C_{12})\text{alkyl}$ ,  $(C_6-C_{10})\text{aryl}$ , or  $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkyl}$ , in which the alkyl and aryl moieties may be optionally substituted,
- xi.  $-(CH_2)_q-(Alk^2)-C(O)-NR^5R^6$  in which  $Alk^2$  and  $q$  are as described above, and  $R^5$  and  $R^6$  are each independently represented by hydrogen,  $(C_1-C_{12})\text{alkyl}$ ,  $(C_6-C_{10})\text{aryl}$ , or  $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkyl}$ , in which the alkyl and aryl moieties may be optionally substituted,
- xii.  $-(CH_2)_q-(Alk^2)-Y-R^7$ , in which  $Alk^2$  and  $q$  are as defined above,  $Y$  is O or S, and  $R^7$  is selected from the group consisting of hydrogen,  $(C_1-C_{12})\text{alkyl}$ ,  $(C_6-C_{10})\text{aryl}$ , or  $(C_6-C_{10})\text{aryl}(C_1-C_6)\text{alkyl}$ , in which the alkyl and aryl moieties may be optionally substituted,
- xiii. heteroaryl, optionally substituted,
- xiv. heteroaryl $(C_1-C_6)\text{alkyl}$ , in which the heteroaryl and alkyl moieties may each be optionally substituted,



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- xv. heterocyclic, optionally substituted,  
xvi. heterocyclic(C<sub>1</sub>-C<sub>6</sub>)alkyl, in which the alkyl  
and heterocyclic moieties may each be substituted, or,

h) for those compounds in which Y is N, X<sup>2</sup> and X<sup>3</sup>, along with the adjacent nitrogen atom, may form a heterocyclic ring, which may optionally be substituted;  
or a salt or solvate thereof.

2. A compound according to claim 1 in which one of R<sup>1</sup> or R<sup>2</sup> is hydrogen and the other of R<sup>1</sup> or R<sup>2</sup> is selected from the group consisting of isobutyl, propyl, n-butyl, isopropyl, and ethyl.
3. A compound according to claim 1 or 2 in which n is 0.
4. A compound according to claim 1, 2, or 3 in which X<sup>1</sup> is trifluoromethyl and is located at the 3-position of the phenyl ring.
5. A compound according to claim 1, 2, 3, or 4 in which Y is NX<sup>2</sup>X<sup>3</sup>.
6. A compound according to claim 5 in which X<sup>2</sup> is hydrogen.
7. A compound according to claim 6 in which X<sup>3</sup> is represented by a substituent selected from the group consisting of (C<sub>1</sub>-C<sub>12</sub>)alkyl, (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, and heterocyclic(C<sub>1</sub>-C<sub>6</sub>)alkyl.
8. A compound according to claim 1, 2, 3, or 4 in which Y is OX<sup>3</sup>.
9. A compound according to anyone of claims 1-8 in which X<sup>1</sup> is represented by halogen or haloalkyl.
10. Use of a compound according to anyone of claims 1-9 as a medicine.

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11. Use of a compound according to anyone of claims 1-9 in the manufacture of a medicament for inhibiting activation of the androgen receptor
12. Use of a compound according to anyone of claims 1-9 in the manufacture of a medicament for the alleviating a condition selected from the group consisting of hormone dependent cancers, benign hyperplasia of the prostate, acne, hirsutism, excess sebum, alopecia, premenstrual syndrome, lung cancer, precocious puberty, osteoporosis, hypogonadism, age-related decrease in muscle mass, and anemia.
13. A pharmaceutical composition comprising a compound according to anyone of claims 1-9 in admixture with 1, or more, pharmaceutically acceptable excipients.
14. A topical pharmaceutical formulation comprising a compound according to anyone of claims 1-9 in admixture with 1, or more, pharmaceutically acceptable excipients suitable for dermal application.
15. An article of manufacture comprising a compound according to anyone of claims 1-9 packaged for retail distribution, which advises a consumer how to utilize the compound to alleviate a condition selected from the group consisting of acne, alopecia, and oily skin.